

A Plan That Establishes a Framework For Achieving Mutual Recognition of Good Manufacturing Practices Inspections

The *Food and Drug Administration Modernization Act of 1997* (FDAMA), November 21, 1997, amended the *Federal Food, Drug, and Cosmetic Act* (FFDCA), 21 U.S.C. 301 et. seq., to require the Food and Drug Administration (FDA) to "make public a plan that establishes a framework for achieving mutual recognition of good manufacturing practices inspections" not later than 180 days after the date of the law's enactment. Pub. L. 105-115 § 410(c)(4), 21 U.S.C. § 383 (c)(4).

Scope of the Plan

The requirement for this plan applies only to mutual recognition of good manufacturing practices (GMP) inspections. However, achievement of mutual recognition requires extensive government to government cooperation that can be facilitated through memoranda of understanding (MOUs) as well as mutual recognition agreements (MRAs) relevant to GMP inspections. The agency has therefore included in this plan information on both MOUs and MRAs. Definitions of these terms are included later in this document.

FDA has a number of arrangements with other countries regarding the exchange of GMP information. The agency's overall strategy is to continue with those activities, learn from that experience, and apply those lessons toward refining and tailoring the key considerations and factors that go into our approach to such arrangements. This document summarizes those activities and presents those factors and considerations.

The plan the agency has developed focuses on FDA's primary role to maintain and strengthen domestic public health safeguards and strives toward a common ground internationally on regulatory systems (including GMPs), criteria for the collection and assessment of inspection information, and appropriate enforcement procedures.¹

Background

FDA has had GMP regulations in effect for many years, and courts have consistently upheld GMP provisions and their application. Adherence to GMPs has long been recognized as critical to ensuring a consistently high level of safety and quality in FDA-regulated products.²

The way goods are produced and regulated in the United States is critical to domestic public health protection. The way goods are produced and regulated in other countries is also increasingly important to public health protection in the United States. As goods move more freely across borders, regulatory agencies and companies are beginning to think of their responsibilities and obligations in more global terms. The globalization of the health products industries presents an opportunity to advance public health protection through various international activities, such as harmonization and equivalence agreements.

Increasingly, FDA finds that it should embark upon activities aimed at expanding its knowledge of the conditions of production or processing of all its regulated products in the country of origin. The agency seeks cooperative initiatives with foreign regulatory authorities to take advantage of a wide array of opportunities for advancing its domestic public health goals through international cooperation and compliance activities, as well as harmonization of regulatory requirements, standards and practices. It is FDA's policy to pursue, with regulatory counterparts in other countries, those agreements that will further the agency's domestic public health mission.

The development of international agreements may be furthered by harmonization. The industries FDA regulates are increasingly multinational in their operations, as companies develop, test, and seek marketing approval for new medical products on a world-wide basis. Internationally harmonized standards for testing, quality and manufacturing have the potential for making product development more efficient and speeding the world-wide availability of new therapies. Harmonization of regulatory requirements or methods, where possible, can reduce paperwork requirements, inadvertent noncompliance, communication errors, and product development time. Counterparts in other countries can help FDA to ensure the safety, effectiveness, and quality of products offered for importation into the U.S., through regulatory oversight of compliance with GMPs.

FDA's strategic plan envisions the development of consistent, harmonized and scientifically-based international standards to keep abreast of the complexity and interface of international health, safety, and commerce issues. Consumers worldwide can have access to safe and effective products without being exposed to unnecessary risks. Further, multiple regulatory requirements on industry can be reduced or eliminated, and industry can be assured that policies affecting international markets will be based on scientifically sound decisions.

FDA participates in international activities, including those of the World Health Organization, to achieve internationally recognized and enforced product safety and efficacy standards, good manufacturing practices, and inspection protocols. The agency believes scientific and regulatory information and knowledge should be exchanged with foreign government officials to the extent possible within legal constraints, to expedite the approval of products and to protect the public health. The agency believes inspection information should be appropriately shared among regulatory authorities, adverse event information should be reported in a timely fashion, and foreign regulatory authorities should collaborate in addressing product safety issues.

FDA cooperates with the international regulatory community to achieve a coordinated program of technical assistance, education, and information exchange. The agency recognizes the tremendous value of technical cooperation with other countries in increasing understanding of regulatory infrastructures, as well as the importance of exchanging inspection information and other documents to facilitate long-term confidence-building in each other's systems. FDA assists in conducting or helping to arrange for training for foreign counterparts to the extent possible with its limited resources.

Resource constraints oblige the agency to focus attention on the highest priority activities and to strive to make its participation in those activities very effective.

Definitions

Some of the terms used when discussing elements necessary for reaching mutual recognition of GMP inspections can have numerous interpretations. In this document, FDA uses the terms as follows:

Memoranda of understanding (MOU): Agreements between FDA and others, including foreign countries, are often called "memoranda of understanding" (MOUs) or, if needed by the foreign counterpart, "memoranda of agreement" (MOAs) or "arrangements," "memoranda of cooperation" (MOCs), or "exchange of letters" (EOLs). Such agreements are used by FDA to document cooperative activities, e.g., information exchange. For convenience, this document uses MOUs as an all-encompassing term.

Mutual recognition agreement (MRA): This term means an agreement between two countries which provides for a reciprocal reliance upon facets of the regulatory system, to the degree specified in the agreement. The requirements being met are those of the importing country, i.e., in the case of the United States, the FFDCA, the Public Health Service Act, and FDA implementing regulations.

Equivalence: With respect to MRAs for GMPs, this term means that the agency has determined that another country's regulatory system for GMPs (i.e., regulations, inspection procedures and enforcement) provides at least the same level of consumer protection as FDA's system.

Harmonization:³ For purposes of discussions on GMP inspections, this concept generally means adoption and application of a common approach to regulatory activities.⁴

FDA's Policy on Agreements with Foreign Regulatory Counterparts

FDA sees value in entering into a variety of agreements with other countries that are consistent with safeguarding the public health and the requirements of U.S. law, to enhance domestic public health protection and facilitate commerce in safe and quality food, drugs, biological products and medical devices. FDA has had a long-standing policy of pursuing the development of such agreements with its counterparts in other countries.

The recently enacted FDAMA specifically includes such activities in the agency's mission. The law directs the agency to "participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal agreements." 21 U.S.C. § 903(b)(3).

FDA's Compliance Policy Guide on *International Memoranda of Understanding*, 60 Fed. Reg. 31485 (June 15, 1995), sets forth the agency's overall policy for developing, initiating, and monitoring MOUs with agencies of foreign governments or international organizations:

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It is the policy of FDA to pursue the development of MOUs that will further the agency's domestic public health mission. MOUs between the FDA and an agency of a foreign government or an international organization should be designed to:

1. Enhance FDA's ability to ensure that regulated products are safe, effective, of good quality, and properly labeled;
2. Allow FDA to utilize its resources more effectively or efficiently, without compromising its ability to carry out its responsibilities; and
3. Improve communication between FDA and foreign officials concerning FDA regulated products.

Further, before accepting the procedures and activities, including enforcement methods, of foreign governments as equivalent to its own, FDA will seek assurance that such activities provide the same level of product quality, safety and efficacy that is provided under the FFDCA; the Fair Packaging and Labeling Act; the Public Health Service Act; and any other relevant law of the U.S. FDA may find it necessary to confirm by on-site review or other appropriate means that the foreign government agency has the necessary authorities, product standards, capabilities, and infrastructure to successfully achieve the proposed terms of the MOU, and, therefore, that a determination of equivalence can be made.

FDA auditing may be necessary to assure that the circumstances supporting the basis for an agreement continue to exist, whether or not the foreign government intends to conduct audits.

FDA's practice is to enter into MOUs for a period of 5 years. MOUs are evaluated at least once during the 5 year period to determine whether the MOU should be modified, or canceled. As part of the evaluation, the agency may conduct independent or joint inspections or analyze imported products to evaluate the effectiveness of the MOU.

The following three categories, described in the 1995 Compliance Policy Guide, CPG 7150.19, serve as examples of types of agreements. They are not mutually exclusive, and can be altered or combined as necessary.

1) Reciprocal Agreements with Countries Having the Same or Similar Systems.

Such MOUs may provide for the mutual assessment for comparability of specific FDA programs or activities with those of a foreign regulatory authority.

2) Certification of Imports/Exports.

MOUs may establish certification criteria for products regulated by FDA. They may identify controls to be employed by the exporting country. The controls will help ensure the validity and reliability of certification to help reduce the FDA rate of inspection or sampling and provide a basis for assurance that FDA's consumer protection objectives are being met.

3) Communications.

Formalizing communication links facilitates the exchange of technical, scientific, and regulatory information. Technical cooperation leads to better understanding of safety and quality standards for products traded between the U.S. and other countries, and promotes harmonization. Improved communications with foreign officials may improve FDA decision making and reduce resource expenditures for monitoring foreign-made products.

Current Agreements and Activities

FDA currently has approximately fifty agreements with its counterparts in other countries. The agency publishes these agreements in the Federal Register (21 C.F.R. § 10.90(d), 20.108), and has also issued a compilation of all such agreements through November 1996 in the FDA *International Cooperative Agreements Manual*.

Examples of existing agreements particularly relevant to GMPs include:

- EOL with Switzerland (1968), on drug inspections.
- MOA with Sweden (1972), on drug inspections.
- Agreement of Cooperation with Canada (1973), on drug inspections.

- MOU with the United Kingdom (1986), on medical device inspections.
- EOL with Australia (1993) on medical device inspections.

In recent years, FDA's essentially constant foreign inspection capacity has been stretched over an expanding volume of imports from foreign countries. Harmonization of regulatory requirements and mutual recognition of GMP inspections with other countries, similar to the agreements mentioned above, can enable FDA to leverage its resources in its efforts to protect the public health. Such efforts advance FDA's domestic public health goals; help it to make efficient use of its scarce resources; and assist the agency in continuing to provide a responsive level of U.S. consumer protection in the face of a rapidly changing global marketplace with inherently variable risks. As an example, one significant activity the agency has recently undertaken in this area is its proposed rule on mutual recognition between FDA and the European Community on conformity assessment procedures, pharmaceutical GMP inspection reports, medical device quality system evaluation reports, and certain medical device premarket evaluation reports. 63 Fed. Reg. 17744 (April 10, 1998).

The agency continues to engage in a variety of activities to advance harmonization⁵ and develop international agreements. Some of these activities are directly relevant to GMPs. To achieve its goal of mutual recognition of GMP inspections with foreign countries, FDA has ensured that its Quality Systems Regulation (Good Manufacturing Practices) for devices (21 U.S.C. Part 820) conforms to the extent practicable with all or part of internationally recognized standards defining quality systems for medical device manufacturers.

FDA has not received additional government funding earmarked for activities aimed at achieving mutual recognition, and it must proceed to implement such efforts within its normal day-to-day regulatory functions and available resources. The pace and priorities for achieving mutual recognition of GMP inspections with foreign countries are dictated by FDA's ability to conduct these efforts concurrently with existing mandates. The need to strengthen surveillance of foreign manufacturers is underscored by a recent General Accounting Office report that called upon FDA to bolster its foreign inspection program to help ensure compliance with United States safety standards. This recommendation applies to manufacturers with a history of substandard manufacturing practices and manufacturers that are increasing their exports to the United States.

Framework for Mutual Recognition Agreements with Other Countries on GMP Inspections

Before FDA can enter into a mutual recognition agreement of GMP inspections with another country, the other country should have in place regulatory requirements for GMPs that are, at least, equivalent to FDA requirements. The country should have in place an adequate regulatory infrastructure in the form of a competent agency, and that agency should have an adequate program of compliance measures.

FDA uses a stepwise approach toward increased confidence in GMP inspections performed by inspectors of other countries. This may start with simple information sharing and can build over time toward normal endorsement of one another's reports of GMP inspections. MOUs can be used as vehicles to achieve one or more of these steps. By contrast, reaching an MRA with another country requires a heavy, up-front level of resource expenditure attendant to mutual recognition. Reaching an MOU that calls for various forms of cooperation, including exchange of information reports upon request or on a routine basis, can be achieved without the level of resource expenditure necessitated in a negotiation leading toward mutual recognition. There are many circumstances in which an MOU is cost effective when an MRA is not. In deciding whether to undertake a process with a foreign country leading toward future mutual recognition of GMP inspections, FDA intends to place emphasis on assessing whether such action will enhance the protection of domestic public health. Analyzing such factors as the following may assist the agency in deciding whether to undertake such a process with another country:

- comparison of regulatory requirements in that country;
- comparison of inspection procedures and enforcement measures;
- existing agreements and other arrangements with that country and resources involved in such agreements;
- consideration of other agreements in progress and associated resource needs with such negotiations;
- impediments to an agreement; and
- the relative priority of this undertaking compared to other agency priorities.

Considerations for Mutual Recognition Agreements

The following considerations are important in determining whether entering an MRA will be of value to FDA in assisting the agency to carry out its responsibilities for protecting the public health:

- The existence of GMP-related risks associated with products exported to the U.S., including the nature and quantity of the products exported.
- The existence of GMP laws and infrastructure for implementation of a GMP inspection program sufficiently similar to FDA's program, that provides a reasonable probability the foreign country's program will be found to be equivalent to FDA's program.
- The degree to which the foreign country implements regulatory requirements in a manner that is the same as, or equivalent to, the manner in which FDA implements its requirements (determined primarily from information obtained from current/recent inspection reports and history of compliance).
- Availability of FDA resources, including administrative and technical personnel, that would be necessary to undertake any required negotiation and equivalence assessment or harmonization activities, if necessary, associated with development of such an arrangement (considering such needs as projected training requirements, on-site review of regulatory systems, and audit inspections).
- The enforcement approaches used to address compliance problems identified and their effectiveness.

Approach for Initiating Confidence-Building Activities with a Foreign Country

The building of confidence over time is the aim of FDA's activities with other countries' regulatory authorities in working toward mutual recognition. When FDA has made a preliminary assessment that a foreign country is interested in, and has the required capacity for, pursuing confidence-building activities, the agency intends to take the following approach:

- development and initiation of an MOU for exchange of inspection reports without first finding equivalence;
- engaging in technical cooperation/support to develop consistency regarding a common base of requirements; collection of the same type and form of information; and assurance that similar information is handled in a consistent manner by both country's regulatory systems;
- seeking opportunities for joint training and inspections;
- encouraging cooperative participation in international harmonization and standards development activities;
- evaluation of regulatory requirements and practices, aiming for
 - common nomenclature
 - common base of actual quality systems/GMP requirements
 - consistent auditing methods, form of written reports, qualification of auditors;
- evaluation of policies and interpretations, aiming for
 - consistency in interpretations of audit reports
 - consistency in determining what is significant enough to take action;
- achievement of long-term mutual confidence in the effectiveness of each other's regulatory system;
- recognition of equivalence of each other's system;
- conclusion of a MRA, establishing mutual recognition of each other's GMP inspections as a general rule, with safeguards upon the agency's ability to do inspections and its right to take appropriate actions to protect the public health.

Current Priorities



FDA's limited resources force the agency to focus on certain high priorities in these general areas which are likely to have the most significant impact on protecting the domestic public health. These areas are as follows:

- Implementing the agreement on mutual recognition between the United States and the European Community. FDA has requested comments on a proposed rule implementing the agreement. 63 Fed. Reg. 17744 (April 10, 1998).
 - Completing harmonization projects essential to the future success of that MRA, e.g., GMPs for active pharmaceutical ingredients, inspectional guides for device GMP inspections.
 - Strengthening long-standing arrangements on exchange of inspection information with other countries.
 - Seeking opportunities for low-cost arrangements for information exchange
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Footnotes:

1. As specified in the FDAMA, the agency will "move toward the acceptance of mutual recognition agreements relating to ... the regulation of good manufacturing practices, between the European Union and the United States." Also under the FDAMA, the agency will "regularly participate in meetings with representatives of other foreign governments to discuss and reach agreement on methods and approaches to harmonize regulatory requirements." Pub. L. 105-115 § 410(c)(2) and (3), 21 U.S.C. § 383 (c)(2) and (3).

2. The use of the term "GMPs" in this plan means current good manufacturing practices. See for example 21 C.F.R. Part 210 on current GMPs in manufacturing, processing, packing or holding of drugs; Part 211 on current GMPs for finished pharmaceuticals; Parts 225 and 226 on current GMPs for medicated feeds; Part 606 on current GMPs for blood and blood components; and Part 820, the quality system regulations for medical devices.

3. FDA announced its policy on the development and use of standards with respect to international harmonization of regulatory requirements and guidelines in a Federal Register notice entitled *International Harmonization, Policy on Standards*, 60 Fed. Reg. 53078, (October 11, 1995). The policy also addresses the conditions under which FDA participates with standards bodies outside of FDA, domestic or international, in the development of standards applicable to products regulated by FDA, including those relating to GMPs.

4. Close cooperation among foreign government regulatory authorities remains essential even when technical regulations are harmonized. Without harmonization, there is limited assurance of similarity in what inspectors look for or in what corrective actions are to be taken.

5. See footnote 3.